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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---------------------------|-------------|----------------------|---------------------|------------------|
| 10/625,847 | 07/24/2003 | Bertrand Pain | 37991-0017 | 8939 |
| 26633 | 7590 | 10/30/2007 | EXAMINER | |
| HELLER EHRLMAN LLP | | | KAUSHAL, SUMESH | |
| 1717 RHODE ISLAND AVE, NW | | | ART UNIT | PAPER NUMBER |
| WASHINGTON, DC 20036-3001 | | | 1633 | |
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| 10/30/2007 | | PAPER | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/625,847 | PAIN ET AL. | |
| | Examiner | Art Unit | |
| | Sumesh Kaushal | 1633 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 22 August 2007.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 58,61,66,68,69 and 72 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 58, 61, 66, 68-69 and 72 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____

5) Notice of Informal Patent Application
6) Other: _____

DETAILED ACTION

Applicant's response filed on 08/22/07 has been acknowledged.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **571-273-8300**.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/27/07 has been entered.

Claim Rejections - 35 USC § 112

Claims 58, 61, 66, 68-69 and 72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature Of Invention

The instant invention relates to a method for producing nonadherent chicken embryonic stem cells capable of proliferating in a basal medium in the absence of exogenous trophic factors any cytokines.

Breadth Of Claims And Guidance Provided in the Specification

The scope of invention as claimed encompasses a method for producing non-adherent chicken embryonic stem cell line capable of proliferating in a basal medium in the absence of all exogenous trophic factors any cytokines.

The specification defines embryonic stem cells (CES cells), are cells that exhibit in-vitro all the characteristics of a stem cell, and in-vivo the unique capacity of contributing to the morphogenesis of an embryo and of participating in germline colonization when they are re-implanted in a recipient embryo (Spec. page 1).

At best the specification provides instructions for culturing a chicken embryonic stem cell line using an inactivated "feeder" composed of mouse fibroblasts cell line (STO cells). The specification further states that under the initial culture conditions, the presence of growth factors is necessary belonging to two families of factors: the cytokines and the trophic factors. The specification teaches that cytokines are LIF, interleukin 11, interleukin 6, CNTF, oncostatin and cardiotrophin. The specification further states that in a few cases, the combination of a soluble form of the receptors, a for interleukin 6 and CNTF, makes it possible to increase the proliferative effect observed. The specification states that the trophic factors are SCF, IGF-1 and bFGF, which are also used at the start of the culture, as described above. The specification states that their presence is also necessary for obtaining and amplifying the cells. The specification projects that by progressively reducing these growth factors, it is possible to obtain, after a few passages, culture conditions which allow the proliferation of the embryonic or somatic stem cells without the addition of an exogenous growth factor (Spec. page 22-23). The applicant argues that instructions provided on page 22 lines 12-25 eables one skilled in the art to produce the desired stem cell lines (Remarks 05/22/07, page 9). However the applicant's arguments are found not persuasive. Applicant's argument alone cannot take place of evidence lacking in the record (see *In re Scarbrough* 182 USPQ, (CCPA) 1979). The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)).

Art Unit: 1633

In the instant case the specification as filed fails to disclose a single non-adherent chicken embryonic stem cell line that is capable of proliferating in a basal medium in the absence of all exogenous trophic factors and cytokines and any feeder layer (see spec. page 30, example 9) and elicits the embryonic stem cells characteristics (*i.e. unique capacity of contributing to the morphogenesis of an embryo and of participating in germline colonization when they are re-implanted in a recipient embryo.*)

Considering the state of art below and limited amount of guidance provided in the specification as filed, it would require an excessive and undue amount to experimentation to produce a non-adherent chicken embryonic stem cells line which is capable of proliferating in any basal medium in the absence of all exogenous trophic factors and cytokines, wherein the embryonic stem cells were initially exposed to exogenous factors (SCF, IGF-1, bFGF, CNTF, IL-6, sIL-6R and IL-11) for at least 20 successive passages in the presence of STO feeder layer.

State Of Art And Predictability

The state of the art at the time of filing teaches that the production of avian cell line especially the embryonic stem cell is considered highly unpredictable. Pluripotent embryonic stem cells are undifferentiated cells capable of proliferation and self-renewal and have the capacity to differentiate into all somatic cell types and the germ line. Pluripotent stem cells in the chick have been derived from stage X blastoderms and 5.5 day gonadal primordial germ cells (PGCs). The potential to give rise to somatic and germ line chimeras is highly dependent upon the culture conditions and decreases with passage. The answers to fundamental questions regarding segregation of the avian germ line and the molecular basis of pluripotency should foster the full use of avian pluripotent stem cells. The main impetus for the isolation and culture of avian embryonic stem cells has been the hope that such cells could be used to generate transgenic birds with specific modifications to the avian genome.

Cultured blastodermal cells from stage IX-XI chick and stage X-XI quail embryos and reported conditions that allowed for the long-term culture of pluripotent embryonic stem cells. Using alkaline phosphatase as a marker of pluripotency, the best results

Art Unit: 1633

were obtained with a combination of human LIF, FGF-2, avian or murine SCF, and IL-11 on a feeder layer of inactivated STO fibroblasts. To neutralize any possible induction of differentiation, an antibody against retinoic acid was also added to the media. Like that observed for mouse ESCs, LIF appeared critical to the long-term proliferation and survival of the cultures. In addition, LIF was required to maintain the expression of several markers associated with an embryonic stem cell phenotype, viz. SSEA-1, EMA-1, and EMA-7. Furthermore, telomerase activity was maintained in the avian ESC cultures after multiple passages, but was down-regulated after a pulse of retinoic acid. Furthermore using heterologous and homologous feeder layers and conditioned media containing variety of factors often produce variable results affecting the long term survival of avian embryonic stem cells.

For example dissociated cells from the un incubated chicken blastoderm at stage X were initially cultured with STO feeder layers, primary chick embryonic fibroblast (CEF) feeder layers, or media conditioned by buffalo rat liver (BRL) cells or by the chicken hepatocarcinoma line LMH could not maintain the blastodermal cells beyond two passages.

Furthermore when the combination of primary CEFs and media conditioned with the LMH cells were used to culture dispersed cells from the area pellucida of the stage X embryo, the cells very quickly differentiated into the primary fibroblast feeder layer. This was unexpected since both primary CEFs and media conditioned with LMH cells are capable of maintaining mouse embryonic stem cells. Therefore the presence of LIF and retinoic acid critically affect the outcome of any culture conditions in order to produce the chicken embryonic stem cells (see Pettie et al, Mech Dev. 121(9):1159-68. 2004, see pages 1161-1162; Pain et al ,Development. 122(8):2339-48, 1996 see page 2341-2343, ref of record, see US 6,998,266, 2006). In the instant case the specification as filed fails to disclose a single non-adherent chicken embryonic stem cell line that is capable of proliferating in a basal medium in the absence of all exogenous trophic factors and cytokines and/or a feeder layer.

Furthermore, considering the scope of the source of the cytokines used, it has been suspected that that mammalian cytokines are not fully effective on chicken ES or

Art Unit: 1633

EG cells given the low identity between chicken and mammalian cytokines. Therefore, it seemed probable that chicken LIF (chLIF) would be more effective in maintaining chicken ES or EG cells in the undifferentiated state than its mammalian homologue. Chicken LIF has been found indispensable for maintaining the undifferentiated state of chicken blastodermal cells in culture (see Horiuchi et al, J Biol Chem. 279(23):24514-20, 2004). Thus the use of particular set of growth factor, cytokines in the presence of STO feeder layer especially in context of instant invention (as claimed) is considered germane to maintain the viable chicken embryonic stem cells

Thus considering the state of the art and limited amount of guidance provided in the instant application is it considered highly unpredictable that one skilled in the art would be able to practice the invention as claimed without further excessive and undue amount of experimentation. Furthermore, It is noted that patent protection is granted in return for an enabling disclosure of an invention; not for vague intimations of general ideas that may or may not be workable (See *Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), *Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

In instant case making a non-adherent chicken embryonic stem cell line capable of proliferating in any basal medium free of all exogenous trophic factors and cytokines is not considered routine in the art and without sufficient enabled disclosure, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant

Art Unit: 1633

specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 58, 61, 66, 68-69 and 72 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 58 in step (a) recites a "primary medium comprising". Since the term "comprising" is considered an open-ended terminology, it is unclear what are other unrecited additional components are there in the context of invention as claimed. see MPEP 2111.03

Claims 61 is indefinite because it is unclear under what conditions "the cells derived from the lines obtained in step (c) are capable, of proliferating for at least 50 days".

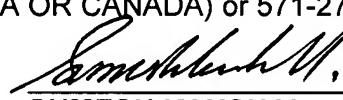
Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


SUMESH KAUSHAL
PRIMARY EXAMINER